

WHAT IS CLAIMED IS:

- 1                   1.       A method for treating cancer comprising administering to a subject  
2   in need of such treatment a therapeutically effective amount of  
3                   (a) a member selected from an inhibitor of inosine monophosphate  
4   dehydrogenase (IMPDH), an enantiomer of such a compound, a prodrug of such a  
5   compound, a pharmaceutically acceptable salt of such a compound, and combinations  
6   thereof; and  
7                   (b) an agent that inhibits a cellular process regulated by GTP or ATP.
- 1                   2.       The method of claim 1, wherein the agent that inhibits a cellular  
2   process regulated by GTP is selected from the group consisting of an inhibitor of  $\alpha$ -  
3   tubulin polymerization, a prodrug therefor, a pharmaceutically acceptable salt thereof,  
4   and combinations thereof.
- 1                   3.       The method of claim 2, wherein the IMPDH inhibitor is selected  
2   from the group consisting of mizoribine, mizoribine aglycone, mycophenolate mofetil,  
3   tiazofurin, viramidine, and ribivarin.
- 1                   4.       The method of claim 2, wherein the  $\alpha$ -tubulin polymerization  
2   inhibitor is selected from the group consisting of indanocene, indanrorine, vincristine,  
3   vinblastine, vinorelbine, combretastatin-A, and colchicine.
- 1                   5.       The method of claim 2, wherein the IMPDH inhibitor is mizoribine  
2   and the  $\alpha$ -tubulin polymerization inhibitor is indanocene.
- 1                   6.       The method of claim 2, wherein the cancer is a slow growing  
2   cancer.
- 1                   7.       The method of claim 6, wherein the slow growing cancer has a  
2   high rate of  $\alpha$ -tubulin turnover.
- 1                   8.       The method of claim 6, wherein the slow growing cancer is  
2   selected from the group consisting of chronic lymphocytic leukemia, chronic  
3   myelogenous leukemia, non-Hodgkins lymphoma, multiple myeloma, chronic

4 granulocytic leukemia, cutaneous T cell lymphoma, low grade lymphomas, slow growing  
5 breast cancer, slow growing prostate cancer, and slow growing thyroid cancer.

1 9. A composition for treating cancer in a subject in need of such  
2 treatment comprising therapeutically effective amounts of

3 (a) a member selected from an inhibitor of inosine monophosphate  
4 dehydrogenase (IMPDH), an enantiomer of such a compound, a prodrug of such a  
5 compound, a pharmaceutically acceptable salt of such a compound, and combinations  
6 thereof; and

7 (b) an agent that inhibits a cellular process regulated by GTP or ATP.

1 10. The composition of claim 9, wherein the agent that inhibits a  
2 cellular process regulated by GTP is a member selected from an inhibitor of  $\alpha$ -tubulin  
3 polymerization, a prodrug therefor, or a pharmaceutically acceptable salt thereof, and  
4 combinations thereof.

1 11. The composition of claim 10, wherein the IMPDH inhibitor is  
2 selected from the group consisting of mizoribine, mizoribine aglycone, mycophenolate  
3 mofetil, tiazofurin, viramidine, and ribivarin.

1 12. The composition of claim 10, wherein the  $\alpha$ -tubulin polymerization  
2 inhibitor is selected from the group consisting of indanocene, vincristine, vinblastine,  
3 vinorelbine, combretastatin-A, and colchicine.

1 13. The composition of claim 10, wherein the IMPDH inhibitor is  
2 mizoribine and the  $\alpha$ -tubulin polymerization inhibitor is indanocene.

1 14. The method of claim 1, wherein the agent that inhibits a cellular  
2 process regulated by GTP is a member selected from a precursor of 9-beta-D-  
3 arabinofuranosylguanine 5'-triphosphate (Ara-GTP), a prodrug therefore, a  
4 pharmaceutically acceptable salt thereof, and combinations thereof.

1 15. The method of claim 14, wherein the IMPDH inhibitor is selected  
2 from the group consisting of mizoribine, mizoribine aglycone, mycophenolate mofetil,  
3 tiazofurin, viramidine, and ribivarin.

- 1                    16.     The method of claim 14, wherein the precursor of Ara-GTP is  
2     selected from the group consisting of guanine arabinoside (Ara-G) and Nelarabine.
- 1                    17.     The method of claim 14, wherein the cancer is a lymphoma or a  
2     leukemia.
- 1                    18.     The composition of claim 9, wherein the agent that inhibits a  
2     cellular process regulated by GTP is a member selected from a precursor of Ara-GTP, a  
3     prodrug therefor, or a pharmaceutically acceptable salt thereof, and combinations thereof.
- 1                    19.     The composition of claim 18, wherein the IMPDH inhibitor is  
2     selected from the group consisting of mizoribine, mizoribine aglycone, mycophenolate  
3     mofetil, tiazofurin, viramidine, and ribivarin.
- 1                    20.     The composition of claim 18, wherein the precursor of Ara-GTP is  
2     selected from the group consisting of guanine arabinoside (Ara-G) and Nelarabine.
- 1                    21.     The method of claim 1, wherein the agent that inhibits a cellular  
2     process regulated by GTP is a member selected from an inhibitor of the *de novo* pathway  
3     of purine biosynthesis, a prodrug therefor, or a pharmaceutically acceptable salt thereof,  
4     and combinations thereof.
- 1                    22.     The method of claim 21, wherein the IMPDH inhibitor is selected  
2     from the group consisting of mizoribine, mizoribine aglycone, mycophenolate mofetil,  
3     tiazofurin, viramidine, and ribivarin.
- 1                    23.     The method of claim 21, wherein the IMPDH inhibitor is  
2     mizoribine.
- 1                    24.     The method of claim 21, wherein the IMPDH inhibitor is  
2     mizoribine aglycone.
- 1                    25.     The method of claim 21, wherein the inhibitor of the *de novo*  
2     pathway of purine biosynthesis is selected from the group consisting of L-alanosine,  
3     methotrexate, trimetrexate, 10-propargyl-5,8-dideazafolic acid (PDDF), *N*-[5-[*N*-(3,4-  
4     dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-*N*-methylamino]-2-thenoyl]-L-glutamic  
5     acid (ZD1694, Tomudex), *N*-[4-[2-(2-amino-3,4-dihydro-4-oxo-7*H*-pyrrolo[2,3-*d*]-

6 pyrimidin-5-yl)ethyl]-benzoyl]-L-glutamic acid (LY231514), 6-(2'-formyl-2'naphthyl-  
7 ethyl)-2-amino-4(3*H*)-oxoquinazoline (LL95509), (6*R,S*)-5,10-dideazatetrahydrofolic  
8 acid (DDATHF), 4-[2-(2-amino-4-oxo-4,6,7,8-tetrahydro-3*H*pyrimidino[5,4,6][1,4]-  
9 thiazin-6yl)-(S)-ethyl]-2,5-thienoylamino-L-glutamic acid (AG2034), and *N*-[5-(2-[(2,6-  
10 diamino-4(3*H*)-oxopyrimidin-5-yl)thio]ethyl)thieno-2-yl]-L-glutamic acid (AG2009).

1                   26.     The method of claim 21, wherein the cancer comprises a  
2 population of cells deficient in the enzyme methyladenosine phosphorylase (MTAP).

1                   27.     A method for treating cancer in a subject in need of such treatment,  
2 wherein the cancer comprises of a population of cells deficient in the enzyme  
3 methyladenosine phosphorylase (MTAP), comprising:

4                   administering to the subject a therapeutically effective amount of a  
5 member selected from an inhibitor of inosine monophosphate dehydrogenase (IMPDH),  
6 an enantiomer of such a compound, a prodrug of such a compound, a pharmaceutically  
7 acceptable salt of such a compound, and combinations thereof.

1                   28.     The method of claim 27, wherein the IMPDH inhibitor is selected  
2 from the group consisting of mizoribine, mizoribine aglycone, mycophenolate mofetil,  
3 tiazofurin, viramidine, and ribivarin.

1                   29.     The method of claim 27, wherein the IMPDH inhibitor is  
2 mizoribine.

1                   30.     The method of claim 27, wherein the IMPDH inhibitor is  
2 mizoribine aglycone.

1                   31.     The composition of claim 9, wherein the agent that inhibits a  
2 cellular process regulated by GTP is a member selected from an inhibitor of the de novo  
3 pathway of purine biosynthesis, a prodrug therefor, a pharmaceutically acceptable salt  
4 thereof, and combinations thereof.

1                   32.     The composition of claim 31, wherein the IMPDH inhibitor is  
2 selected from the group consisting of mizoribine, mizoribine aglycone, mycophenolate  
3 mofetil, tiazofurin, viramidine, and ribivarin.

1                   33.     The composition of claim 31, wherein the inhibitor of the de novo  
2 pathway of purine biosynthesis is selected from the group consisting of L-alanosine,  
3 methotrexate, trimetrexate, 10-propargyl-5,8-dideazafolic acid (PDDF), *N*-[5-[*N*-(3,4-  
4 dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-*N*-methylamino]-2-thenoyl]-L-glutamic  
5 acid (ZD1694, Tomudex), *N*-[4-[2-(2-amino-3,4-dihydro-4-oxo-7*H*-pyrrolo[2,3-*d*]-  
6 pyrimidin-5-yl)ethyl]-benzoyl]-L-glutamic acid (LY231514), 6-(2'-formyl-2'naphthyl-  
7 ethyl)-2-amino-4(3*H*)-oxoquinazoline (LL95509), (6*R,S*)-5,10-dideazatetrahydrofolic  
8 acid (DDATHF), 4-[2-(2-amino-4-oxo-4,6,7,8-tetrahydro-3*H*pyrimidino[5,4,6][1,4]-  
9 thiazin-6yl)-(S)-ethyl]-2,5-thienoylamino-L-glutamic acid (AG2034), and *N*-[5-(2-[(2,6-  
10 diamino-4(3*H*)-oxopyrimidin-5-yl)thio]ethyl)thieno-2-yl]-L-glutamic acid (AG2009).

1                   34.     The composition of claim 31, wherein the inhibitor of the de novo  
2 pathway of purine biosynthesis is L-alanosine.

1                   35.     The method of claim 1, wherein the agent that inhibits a cellular  
2 process regulated by GTP is an antagonist of a G-protein coupled receptor (GPCR).

1                   36.     The method of claim 35, wherein the IMPDH inhibitor is selected  
2 from the group consisting of mizoribine, mizoribine aglycone, mycophenolate mofetil,  
3 tiazofurin, viramidine, and ribivarin.

1                   37.     The method of claim 35, wherein the GPCR antagonist is selected  
2 from the group consisting of atrasentan, leuprolide, goserelin, and octreotide.

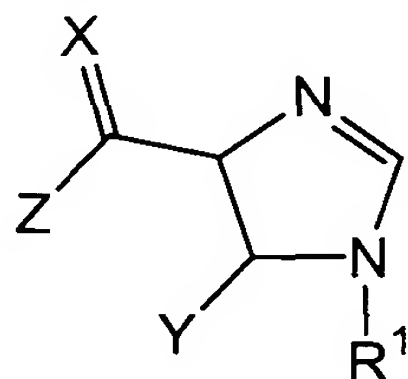
1                   38.     The method of claim 35, wherein the cancer is prostate cancer.

1                   39.     The composition of claim 9, wherein the agent that inhibits a  
2 cellular process regulated by GTP is a member selected from an antagonist of a G-protein  
3 coupled receptor (GPCR), a prodrug therefor, or a pharmaceutically acceptable salt  
4 thereof.

1                   40.     The composition of claim 39, wherein the IMPDH inhibitor is  
2 selected from the group consisting of mizoribine, mizoribine aglycone, mycophenolate  
3 mofetil, tiazofurin, viramidine, and ribivarin.

1                    41.     The composition of claim 39, wherein the GPCR antagonist is  
2     selected from the group consisting of atrasentan, leuprolide, goserelin, and octreotide.

42.     A compound having the formula:



wherein

R<sup>1</sup> is a member selected from H, substituted or unsubstituted alkyl,  
substituted or unsubstituted heteroalkyl and saccharyl moieties;

X is a member selected from O, S and NR<sup>2</sup>

in which

R<sup>2</sup> is a member selected from H, substituted or unsubstituted alkyl,  
substituted or unsubstituted heteroalkyl, OH and NH<sub>2</sub>;

Y is a member selected from OR<sup>3</sup> and NHR<sup>3</sup>

in which

R<sup>3</sup> is a member selected from H, substituted or unsubstituted alkyl,  
substituted or unsubstituted heteroalkyl, acyl and  
P(O)OR<sup>12</sup>R<sup>13</sup>

wherein

R<sup>12</sup> and R<sup>13</sup> are members independently selected from H,  
substituted or unsubstituted alkyl, substituted or  
unsubstituted heteroalkyl, acyl, acyloxyalkyl, and a  
single bond to an oxygen of said saccharyl of R<sup>1</sup>;

Z is a member selected from NR<sup>4</sup>R<sup>5</sup>, OR<sup>4</sup> and SR<sup>4</sup>

in which

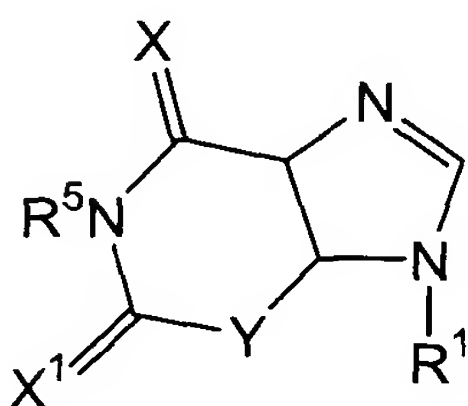
R<sup>4</sup> is a member selected from H, substituted or unsubstituted alkyl,  
substituted or unsubstituted heteroalkyl, a single bond to R<sup>3</sup>  
and acyl;

R<sup>5</sup> is a member selected from H, substituted or unsubstituted alkyl,  
substituted or unsubstituted heteroalkyl, acyl,

acyloxycarbonyl, amino acid, peptidyl and acyloxyalkyl moieties; and

$R^3$  and  $R^4$ , together with the atoms to which they are attached, are optionally joined to form a 6-membered heterocyclic ring; when  $R^3$  is  $P(O)OR^{12}R^{13}$ , and  $R^1$  is a saccharyl moiety,  $R^{13}$  and said saccharyl moiety and the atoms to which they are attached are optionally joined to form an 8-membered heterocyclic ring, with the proviso that said compound includes at least one of said 6-membered or said 8-membered heterocyclic ring system.

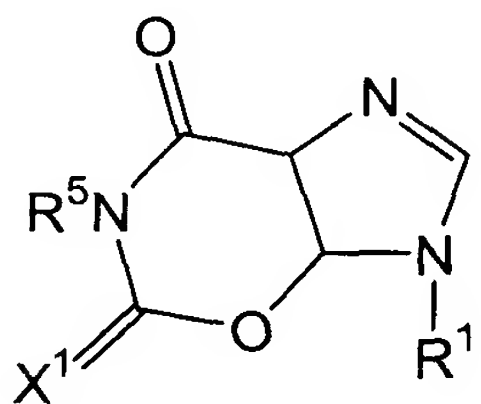
43. The compound according to claim 42, having the formula:



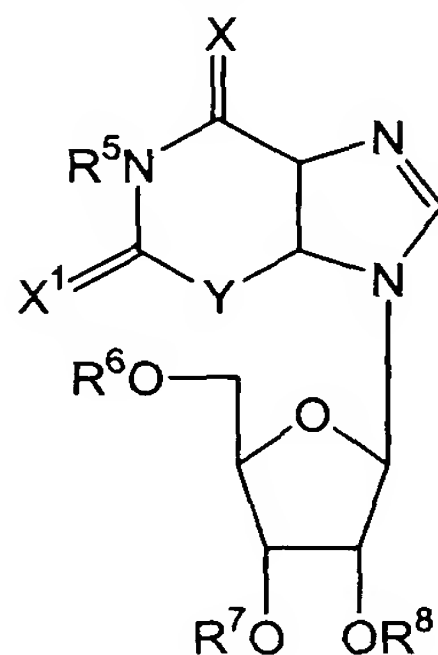
in which

$X^1$  is a member selected from O and S.

44. The compound according to claim 43, having the formula:



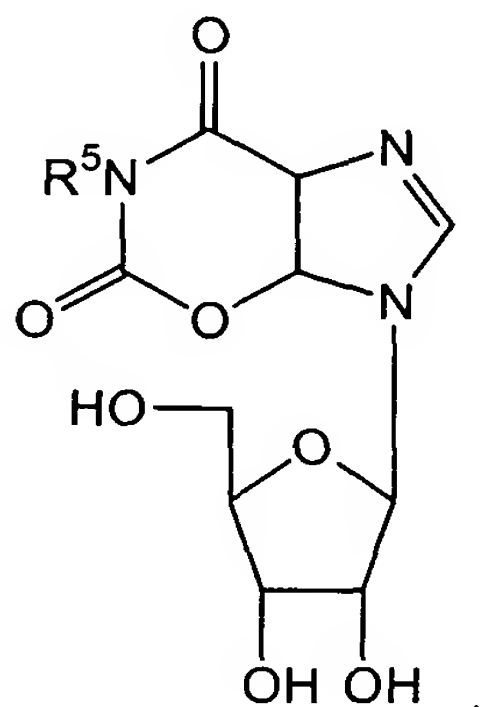
45. The compound according to claim 43 having the formula:



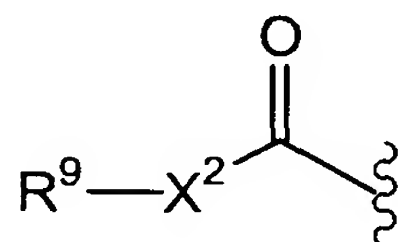
wherein

$R^6$ ,  $R^7$  and  $R^8$  are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl and acyl moieties.

46. The compound according to claim 45 having the formula:



47. The compound according to claim 42, wherein  $R^5$  has the formula:



wherein

$X^2$  is a member selected from O,  $CHR^{10}R^{11}$ , and  $OC(O)$

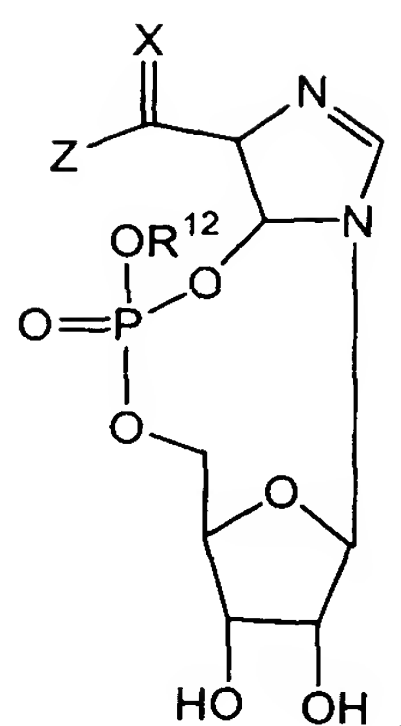
wherein

$R^{10}$  and  $R^{11}$  are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl,  $NH_2$ ,  $NH_3^+$ ,  $COOH$ ,  $COO^-$ , OH, and SH; and

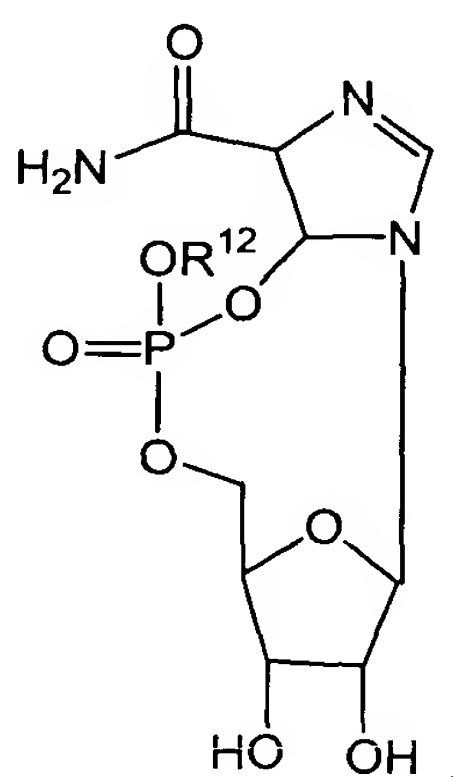
$R^9$  is a member selected from H, substituted or unsubstituted alkyl, and substituted or unsubstituted heteroalkyl.

48. The compound according to claim 42 having the formula:





49. The compound according to claim 48, having the formula:



- 1                    50.     A pharmaceutical formulation comprising a compound according  
2     to claim 42 and a pharmaceutically acceptable carrier.
- 1                    51.     A method for treating cancer comprising administering to a subject  
2     in need of such treatment a compound selected from the group consisting of mizoribine,  
3     mizoribine aglycone, prodrugs of mizoribine, and prodrugs of mizoribine aglycone ,  
4     wherein the compound is administered in an amount sufficient to maintain a plasma level  
5     of the compound of between 0.5 and 50 micromolar for between 6 and 72 hours.
- 1                    52.     The method of claim 51, wherein the plasma level of compound is  
2     between 1 and 30 micromolar for between 8 and 48 hours.
- 1                    53.     The method of claim 51, wherein the plasma level of compound is  
2     between 5 and 25 micromolar for between 10 and 24 hours.
- 1                    54.     The method of claim 51, wherein the plasma level of compound is  
2     at least 10 micromolar for at least 12 hours.

1                    55.     The method of claim 51, wherein the compound comprises a  
2     pharmaceutically acceptable carrier.

1                    56.     The method of claim 51, wherein the compound is administered  
2     parenterally.

1                    57.     The method of claim 51, wherein the compound is administered  
2     orally.

1                    58.     The method of claim 51, wherein the compound is described by the  
2     formula of claim 42.

1                    59.     A method of treating an immune system condition by providing an  
2     immunosuppressive agent, the method comprising administering to a subject in need of  
3     such treatment a therapeutically effective amount of a compound described by the  
4     formula of claim 42.

1                    60.     The method of claim 59, wherein the compound comprises a  
2     pharmaceutical carrier.

1                    61.     The method of claim 59, wherein the immune system condition is  
2     rejection of a transplanted organ.

1                    62.     The method of claim 59, wherein the immune system condition is  
2     an autoimmune disease.